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HEREDITY FROM THE PHYSICO-CHEMICAL POINT OF VIEW.[1]

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Heredity, the power of reproducing its like, is a property of all forms of living matter from the lowest to the highest. Broadly speaking, whenever a universal property or mode of action is found, the presumption is that its basis is fundamentally *simple*, for repetition is characteristic of simple rather than of complex conditions and objects in nature: in general, the fewer the variables the more constant the phenomenon. We have therefore to seek for some general or fundamental structural or physico-chemical peculiarity of living things which enables their substance to build up substance of a similar kind. Any form of protoplasm acts as a center of construction of similar forms. At present we are not concerned with the further fact that this reduplication is not perfect, that varieties appear and that diversity has arisen in the course of evolution. This process of divergence is gradual, and even in mutants the differences from their parents are slight compared with the resemblances; the essential fact is that the type is preserved, and that normally the organism appears unable to construct living matter of other than its own kind. The main question is why any species of organism tends so strongly to retain its specific character.

Apparently the most universal property of living matter is its power of proliferation. Out of materials and energy taken from the surroundings it constructs more living matter of the same kind. In other words, the power of *growth* is innate; and if the available nutritive and other materials are sufficient the quantity of the specifically organized and active living substance tends continually to increase. The degree of increase possible under

[1] From the Laboratory of General Physiology, Clark University.

the conditions may be limited; and in fact most individual organisms and cells have definite limits of size, a balance being eventually reached where metabolic destruction balances construction; nevertheless the construction of new living substance, the essential process underlying growth, continues in all cases throughout life, and when it ceases, life ceases; the constructive process cannot suffer permanent interruption. Even where the organism as a whole seems to have reached its final dimensions there are always special cells or regions which when placed under appropriate conditions still show indefinite proliferative activity. In higher organisms such regions are represented more especially by the germinal epithelium; and a single detached cell from this region exhibits under certain conditions that unique property of definite and orderly proliferation known as development, which leads to the production of an organism similar in its minutest details to that of which the cell originally formed part. This is the chief form which the process of reproduction takes in higher animals, and such a manner of consideration shows that no fundamental distinction can be drawn between growth and reproduction. In many organisms almost any portion of sufficient size which is detached from the whole—whether by some physiologically normal mechanism like fission or as the result of operation—may continue its growth after isolation, redifferentiate, and eventually regain the form and physiological characters of the original stock. Whole plants may thus be reproduced from artificial cuttings, and the same is true of many lower animals (protozoa, hydroids, planarians). In such cases the distinction between growth and reproduction becomes ill-defined, and reproduction appears as essentially a form of discontinuous growth; and in an organism like yeast, where the growing cell-masses may either cohere in chains or fall apart into separate cells—apparently as the result of purely casual conditions—the distinction ceases to have more than a formal significance. If the cell-chain is regarded as the unit organism, increase in its length by budding is a matter of *growth*; if the single cell is so regarded, the same phenomenon becomes an instance of *reproduction*.

It is important for the purpose of the present discussion that the artificiality of this distinction should be recognized at the

beginning, in order that the nature of the essential problem should be clearly defined. Our aim is to analyze into its simplest physico-chemical terms—so far as this is possible at present—this power of specific construction, of structural and chemical synthesis, which is possessed by all forms of living matter. Reproduction and growth are different manifestations of the same proliferative process. Gametic reproduction is, to be sure, the most highly involved and specialized form of proliferation which we know; yet even here, as also in the case of a simple yeast-cell or bacterium growing in a culture-medium, the process of construction is accomplished through the action of the original germ in incorporating and transforming physically and chemically, in a definite and specific manner, certain materials (food, water, salts, oxygen) taken from the surroundings. The problem of just why the complex and highly organized living system thus built up from a particular species of egg-cell should exhibit its own specific structural, physiological, and chemical peculiarities, and why these should be identical with those of the parent, is one which can be solved in detail only by the special investigation of that particular species. But the fact that any such special development is a prolonged and complex process, involving a progressively increasing differentiation and at length reduplicating the parent form, does not alter its general character as proliferation. The fundamental *general* problem remains the same, whether the process under consideration is the formation of new yeast-cells or bacteria in a culture medium, or the development of a higher animal from a fertilized egg. In both cases material from the surroundings is transformed into living specifically organized substance of a constitution identical with that of the parent organism. And we have to ask whether it is possible, in the present state of our knowledge, to form any clear and consistent conception of the general nature of the physico-chemical conditions under which such a result is accomplished.

A simple concrete instance will define more clearly the nature of the problem to be solved. Consider the case of a single yeast cell introduced into a culture medium. The cell grows and forms buds; these give rise to other buds, and cell-chains are formed from which single cells detach themselves and pass

through similar transformations; eventually in place of the original cell there are thousands. The non-living material of the culture medium—consisting of water, sugar, ammonium tartrate, and inorganic salts of potassium, calcium, iron, and magnesium—has been transformed into complex and active living protoplasm of a specific chemical and structural organization. Each living cell exhibits the "germ-action" so characteristic of life—*i. e.*, acts as a center of chemical and physical transformation of a definite kind by which more and more yeast protoplasm is formed. We may note here the analogy—to which we shall return—with the process of specific accretion by which a crystal introduced into a super-saturated solution increases its size and becomes a center of deposition of more crystals of the same kind. But the analogy is incomplete; the living organism does not merely change the physical state of the substances which it takes in from the surrounding solution; it also modifies them chemically in the most profound manner, and from the above simple materials it builds up proteins, lipoids, fats, glycogen, and a multiplicity of other substances not present in the culture medium. Further, not only are these substances synthesized, but they are distributed throughout the growing mass of protoplasm in a perfectly definite manner, partly as solid structural material, partly as dissolved or other material serving for energy-production or some form of metabolism.[1] Each one of the specific organized structures thus produced, the yeast cells, reduplicates the physiological activities as well as the structural characters of the parent cell. The result is that the non-living material of the surroundings is transformed or worked over into organized living material of a predetermined type, *i. e.*, the transformation is *specific* and depends upon the nature of the germ originally introduced into the medium. Both growth and heredity are exemplified in their simplest manifestations; and we see again that these terms do not signify two objectively different processes, but merely two aspects of the same process—"growth," the quantitative term, denoting the increase in the total mass of living substance, while "heredity" emphasizes the specificity of the process and its dependence upon the parental character.

[1] *I. e.*, the problem of *differentiation* is inseparable from the problem of growth.

It is possible to say that each yeast cell *inherits* its properties from the mother cell; but such a phrase serves merely to indicate that the character of the transformation depends upon the character of the germ or proliferating organism itself, rather than upon the character of the material which is transformed under its influence. A mould or bacterium in the same medium effects a totally different kind of transformation, but one equally specific and equally true to the character of the introduced germ.

In general the possession of this automatic property of specific structural and chemical synthesis constitutes the most fundamental distinction between the living and the non-living material systems found in nature. We observe that all organisms and all living cells without exception possess this power; they transform certain inert materials selected from the surroundings into their own characteristically organized and physiologically active living substance. The materials thus incorporated and transformed differ widely in their character and accessibility in different organisms; at the one extreme are green plants living on carbon dioxide, salts, and water; at the other extreme is man in his complex social environment. But this difference of degree does not alter the fundamental identity of kind. Wherever we find life we find exhibited this unique property of specific construction or synthesis, whether the product of the construction is simple or complex.

This property also manifests itself in another and less evident manner. The specific organization of any animal or plant, with the associated physiological activity, not only *originates* in this manner as the product of growth from the parent organism, but once reached, it has to be *maintained*. And this maintenance involves the activity of specific construction in just as full a sense as does growth or development from the germ. During life the organized living substance is continually being destroyed, and must as continually be replaced. This becomes especially evident in certain of the lower animals whenever the food-supply is withdrawn; the quantity of living substance then undergoes progressive reduction, which may proceed until only a small fraction of its original quantity is left; a planarian may thus be reduced by starvation to a quarter of its original length without

injury, but disorganization and death follow further reduction unless food is restored. A similar loss of living substance through the destructive metabolism inseparable from the life-process takes place in all cells, although its rate and its possible limits vary in the different cases—apparently because of the unequal resistance of different structural elements to regression of this kind; thus in higher animals the loss during starvation is great in voluntary muscle and small in the heart and nervous system. In all cases the specific structural material appears subject to a certain continual breakdown of this kind; even when the non-nitrogenous food-supply is ample for energy-requirements it is found impossible to reduce the nitrogen metabolism—the index of destruction of protein, the specific structure-forming substance—below a certain well-defined minimum. This can only mean that the structural or organized material is subject to continual destruction, and that maintenance involves its continual replacement. This process of replacement is specific, in precisely the same sense in which the growth-process is specific. We must therefore recognize that maintenance involves the activity of specific chemical and structural synthesis in the same sense as does growth. When the construction of organized substance balances destruction there is equilibrium—the condition corresponding to nitrogenous equilibrium in higher animals; any excess of construction leads to growth, of destruction to regression. We see once more that what is essential to continued life is the specific synthetic activity of the protoplasm; when this ceases, life ceases. Claude Bernard expresses this necessary dependence of life upon synthetic or creative processes in the phrase, "life is creation." It is clear that the process of specific creative synthesis which lies at the basis of heredity is inherent in the life-process in all of its forms. The problem of heredity is not a problem to be dealt with by itself; it becomes identical with the most fundamental problem of general physiology, the problem of how living protoplasm is synthesized from non-living matter.[1]

[1] All of this is clearly recognized by Claude Bernard; *cf.* "Leçons sur les phénomènes de la vie," Vol. 2, p. 517, where he summarizes his general view as follows: "The synthetic action by which the organism thus maintains itself [*i. e.*, by a combination of chemical and formative synthesis] is at bottom of the same nature as that by which it repairs itself after it has undergone mutilation, or still further,

The general physiological problem presented by the phenomena of growth and heredity thus reduces itself to these terms: what are the essential physico-chemical conditions upon which this power of specific construction depends? It seems clear that only a thorough knowledge of the conditions determining the special type of metabolism involved in the process, and especially of its constructive side, can answer such a question. The living organism or cell is primarily a metabolizing system. Growth is the expression or result of a process of metabolism; both the material and the energy required for growth come from outside; within the organism they are transformed in such a manner as to build up an organized system of predetermined kind, the seat of chemical and physical processes which maintain the system and enable it under appropriate conditions to increase in size or to produce other similar systems leading independent life.

In all organisms constructive metabolism involves the synthesis of a multiplicity of new chemical compounds from the food and other materials furnished by the surroundings. The food-materials are typically non-specific in their chemical nature, *i. e.*, they show no relation to the specific character of the organism utilizing them; they are either chemically simple in themselves, or become so during incorporation. In animals, where the organism receives part of its food in highly specific form, as protein, all specificity is invariably lost in the hydrolytic processes of digestion; the material before becoming available for nutrition is reduced to a form in which it can be utilized indifferently by all cells. This non-specificity of the food-materials, as they reach the cells, is in striking contrast with the specificity of the compounds built up from them within the cells. Reduction to a simple or non-specific state is thus the indispensable preliminary to the constructive process. It is therefore highly significant that the chief structural colloids, the proteins, are so readily transformed from the specific to the non-specific state.

by which it grows and reproduces itself. Organic synthesis, generation, regeneration, maintenance, healing of wounds, are different aspects of an identical phenomenon, are varied manifestations of the same agent. . . ." In the Presidential address of J. S. Haldane before the British Association in 1908 (Nature, Vol. 78, p. 555) a similar point of view is expressed, *e. g.* "nutrition itself is only a constant process of reproduction .... Heredity is for biology an axiom and not a problem."

The universal presence of proteases in cells seems to be the expression of this necessary condition, since in all cells the structural proteins are capable (under certain conditions) of regression and translocation, *i. e.*, of being utilized as food-material elsewhere—the proteins of one region of the cell or organism acting as reserve, so to speak, for construction at other regions. Such a condition is apparently necessary for the normal regulation of cell-structure and activities. For the continuance of normal cell-activity a proper ratio between structural and metabolizing substance must be preserved;[1] hence in every cell the conditions must be present for reducing proteins and other materials to a non-specific and diffusible form, in addition to the conditions for specific synthesis.

By the synthetic activity of the protoplasm these relatively simple substances are united and chemically remodeled so as to form a variety of more complex compounds of which the most individualized and specific are the proteins. The term *specific* is here used as meaning peculiar to the particular organism or cell under consideration, and not occurring elsewhere. It is not a coincidence that living organisms, the most complex systems, in the structural sense, occurring in nature, are also the most complex in the purely chemical sense; and all of the evidence indicates that the structural complexity is the expression or consequence of the chemical complexity.[2] The essential reason for this appears to be that a high degree of chemical specificity or individualization is the necessary prerequisite for structural complexity, and that chemical specificity depends largely upon peculiarities of stereochemical configuration. The number of individualized isomers in the case of any organic compound increases rapidly with increase in the number of asymmetric carbon atoms in the molecule. Hence the proteins, formed of linked amino-acids, most of which are asymmetric compounds, exhibit the possibilities of chemical individualization to a greater degree than any other known class of compounds. It is further significant that proteins which are specifically distinct chemi-

[1] *E. g.*, in a starving protozoön or planarian the normal structure and proportions are preserved, in spite of the decrease in size.

[2] Similarly with structural diversity, whether in the same organism or in different organisms. A corresponding chemical diversity is implied.

cally, although otherwise closely similar—*e. g.*, hæmoglobins from different species—tend to form crystals, *i. e.*, structural aggregates, which are specifically distinct in their form-characters.[1] A definite relation between the chemical specificity and the structure-forming properties of these colloids is thus indicated. The relation of proteins to organic structure therefore requires special consideration in any theory of heredity.

The proteins form the colloids out of which, together with certain other associated materials, chiefly lipoid, the more permanent or stable, *i. e.*, "structural" portions of most living organisms, and especially the cell-structures, are built up. The relations of these substances to the specific characters of the organism must for this reason be recognized as peculiarly intimate, even though we are not yet in a position to understand the exact relationship between a particular type of structure in an organism and the specific peculiarities of the protein composing that structure. The available evidence indicates, however, that a definite relationship of this kind does exist. We know for example that the presence of foreign proteins is often incompatible with the preservation of normal structure in cells; the cytolytic action of foreign blood-sera, and the formation of specific cytolysins when cell-proteins are used as antigens, show that so fundamental a character as the semi-permeability of the plasma-membrane in a cell is dependent upon the specific peculiarities of its constituent proteins. And in all cell-structures it is probable that a similar relation exists. Such facts indicate clearly that the specific structure of a cell or organism depends upon the chemical specificity of its structural proteins. Now the term specificity, as applied to the individualized character of an organic species, has its morphological and physiological as well as its chemical significance: *i. e.*, each species has its own special form and structure and its own characteristic modes of activity and behavior, as well as its own distinctive and unique chemical composition. But according to the present conception it is the *chemical* specificity which forms the basis of the other two, and

[1] *Cf.* Reichert and Brown: "Differentiation and Specificity of Corresponding Proteins and other Vital Substances in Relation to Biological Classification and Organic Evolution: the Crystallography of Hæmoglobins." Carnegie Institution of Washington, 1909.

chemical specificity is primarily the property of the proteins. Other biochemical compounds appear to be chemically the same wherever found, but the proteins vary in their specific character from species to species. Moreover, physiologically corresponding or "homologous" proteins are more nearly alike in their chemical and physical characters the more closely related the species are from which they are taken. There is thus a general parallelism between the degree of chemical relationship exhibited by homologous proteins from different organisms, and the degree of biological relationship existing between the species. The indications of this are too various to present in detail in this brief paper, and the evidence has recently been reviewed in an admirable manner by Loeb in his "Organism as a Whole."[1] The specificity which such proteins exhibit when used as antigens, *e. g.*, in the formation of precipitins or specific cytolysins, or in the phenomena of anaphylaxis, shows clearly that the proteins of one species are chemically distinct from the corresponding proteins of even nearly related species, and still more distinct from those of more distant species. Nuttall's well-known work shows that the ability of a given precipitin to react with and precipitate its corresponding protein from another species is a close indication of the degree of blood-relationship between the species under consideration.[2]

Apart from these facts, whose significance in relation to the present problem is now well recognized, there are other evidences of chemical specificity in proteins that offer clearer indications of the nature of the connection between the chemical character of a protein and the character of the structures which it forms in the living cell. The work of Reichert and Brown has shown that hæmoglobin crystals from a given species exhibit form-characters which are definite and specific for the species. This means that when the protein separates from solution in the process of crystallization the molecules, as they unite to form larger crystalline aggregates, by degrees build up structures with definite form-characters—the typical forms of one species exhibiting constant differences from those of other species, even of

[1] *Cf.* Chapter 3: "The Chemical Basis of Genus and Species."

[2] Nuttall, "Blood Immunity and Blood Relationships." Cambridge University Press, 1904.

the same genus. The growing crystal takes on a definite "species-specific" form, in a manner suggesting a close analogy to the growing germ; this definite form is the expression of the specific properties of the protein molecule, and is presumably dependent upon its special stereochemical configuration. It is well known that molecules of similar stereo-structure tend to segregate in the process of crystallization; thus in the crystallization of a racemic tartrate from its solution one group of crystals is formed exclusively—or at least predominantly—of molecules of the dextro-tartrate, the other of the lævo-tartrate, although in respect to solubility and other physico-chemical properties the two compounds are identical. In such an instance it is quite certain that similarity of stereo-structure is the critical factor determining the union of the dextro-molecules to form a definite crystalline aggregate specifically distinct from that formed by the lævo-molecules.[1]

The physiological properties of the two stereo-isomers are correspondingly unlike; fermentability and related properties (such as general assimilability and pharmacological action) have been shown to differ markedly in a large number of pairs of asymmetric compounds, a clear proof that the activity of living protoplasm is largely conditional upon the specific space-relations of the atoms composing the physiologically active molecules. This is particularly true of compounds entering into metabolism: thus we know that enzyme action is determined by stereo-structure. Perhaps the clearest proof that specific constructive metabolism is similarly determined is furnished by the specific character of the metabolic response following the introduction of protein antigens into the organism—*i. e.*, by the specific character of the anti-bodies produced. These new compounds, evidently synthesized by the living cells, exhibit specific chemical

[1] Thus the introduction of a crystal of the lævo form into a supersaturated solution of racemic tartrate causes the separation of lævo-tartrate alone; similarly dextro-crystals separate out dextro-tartrate (*cf.* Gernez: Comptes rendus, 1866, Vol. 63, p. 843). The recent work of Marc indicates that in general crystallization is preceded by an adsorption; and that crystals, when used as adsorbents, adsorb by preference substances which crystallize in a similar form. *I. e.*, the similarity in the spatial configuration of the molecules is what determines their union to form larger aggregates (*cf.* Marc: Zeitschr. physik. Chem., 1913, Vol. 81, p. 641; also *ibid.*, 1911, Vol. 75, p. 710, and earlier papers there cited).

properties which are directly determined by the specific properties of the foreign protein introduced. The intimate relationship between the phenomena of immunity and the phenomena of normal assimilation has been pointed out by Ehrlich and others. And since heredity is primarily a matter of assimilation—*i. e.*, construction of the like—it seems clear that the construction of specific protein in the normal processes of growth is the expression of a similar determination of specific constructive processes in the cell by means of the proteins *normally* present. In other words, *the structural proteins already present must determine the production of similar proteins.*

The above tendency of structurally similar compounds to form aggregates when they separate from solution is probably the essential reason why the proteins native to the cell—already forming part of its structure—undergo increase in quantity, with the result that the cell grows. Nothing less than this is to be inferred from the fact that proteins form the basis of specific structures, and that the preservation of the normal characters of any living cell depends upon the continual formation and reformation of these particular compounds. Those proteins which are already laid down as structure within the living cell are thus to be regarded as acting as centres of deposition of further protein identical in composition and configuration. It seems necessary also to conclude that these same structural proteins directly control or guide the actual synthetic process by which more protein of the same kind is built up, presumably by the dehydrolytic condensation of the amino-acids present in the protoplasm. The precise and specific mode of union corresponding to any particular structural protein would then be determined by the specific character of the protein itself. Such a conception would correspond to that of specific catalyzers—the usual manner of conceiving these phenomena at present—the only difference being that the structural protein would itself play the part of catalyzer. Such a process would constitute a form of autocatalysis; the resemblance of growth to an autocatalytic process has in fact been emphasized by Loeb, Robertson, and others.[1] The structural

[1] *Cf.* J. Loeb, *Biochem. Zeitschr.*, 1906, Vol. 2, p. 41. T. B. Robertson, *Arch. f. Entwicklungsmech.*, 1908, Vol. 25, p. 581. Wfg. Ostwald: Roux's *Vorträge und*

peculiarities of such deposits, and hence the specific morphological characteristics of the cell, would be determined by the specific chemical characteristics of the constituent proteins, in a manner analogous to that by which the special form of a hæmoglobin crystal-aggregate is determined. And the special character of the structure thus laid down would determine the special character of the metabolism, and hence the special type of physiological activity exhibited by the cell. This last conclusion seems inevitable, since the source of this activity is metabolism, which in all living systems is under the control of structure. In other words, the formation of a specific structure in the protoplasmic substratum will necessitate a correspondingly specific type of metabolism, since the nature and rate of the metabolic chemical reactions are controlled by the structural conditions present; the dependent physiological or functional manifestations must therefore also be specific.

We are thus led to conceive certain features of the organic formative process in a somewhat definite manner, which may be summarized briefly as follows: The specific characters of any animal or plant are determined ultimately by the specific characters of its structure-forming proteins. The developing germ or the growing organism synthesizes specific proteins, and these, since they determine the structural and hence the physiological peculiarities of the organism, form the basis of its special character as an organic species. Accordingly one of our most fundamental problems is to determine why the cell builds up proteins of its own specific type. The essential problems of heredity and reproduction center here. As we have seen, heredity is exemplified whenever one yeast-cell or bacterium gives rise to another; also whenever any cell grows and increases its living organized material. This increase in living material is indispensable for the continuance of the species, and for this reason we may characterize growth as the fundamental life-process, and the problem of growth in its most general aspect as identical with the problem of heredity. The factors of growth are the factors of heredity.

Aufsätze, Heft 5, 1908. Chodat made a similar suggestion for plant growth in 1905 (*cf.* D'Arcy Thompson: "Growth and Form," Cambridge Univ. Press, 1917, p. 132).

Such a conclusion directs our particular attention to the general nature of the conditions controlling growth.

Growth and development may be controlled to a greater or less degree by various artificial means; and much of experimental embryology is concerned with modifying the rate and character of either process. In this way many definite hereditary characters may be profoundly altered, or in some instances their appearance may be altogether suppressed. A simple and instructive instance is described by Loeb.[1] The sea-urchin egg will develop to the gastrula stage in a balanced solution of sodium, potassium, and calcium chloride; if in addition to these salts some sodium carbonate is present, the skeletal spicules may form and a pluteus larva develop, but not otherwise. The skeleton is an inherited character; its formation, however, is dependent upon the presence of sodium carbonate in the surrounding medium, as well as upon the organization of the germ; the necessary carbonate must be furnished to the germ from without, or the specific formative process is unable to take place. Such a result is not difficult to understand. Development, like growth, is a matter of metabolism, and primarily of constructive metabolism; hence it is influenced by any condition that influences metabolism; accordingly the presence or absence of food, oxygen, water, salts, vitamines, hormones, as well as the conditions of temperature, may each and all have determinative relations to the total process. It is significant, however, that the specific characters of the organism, those which, according to the present view, express the chemical specificity of its structural proteins, seem never to be essentially altered by such changes of condition, although their appearance may be prevented or the degree of their development modified. Whatever structural characters appear in development are those characteristic of the species; this statement may be qualified to the degree required to take into consideration the facts of mutation (these suggest that under exceptional conditions new structural proteins may be synthesized); but the essential fact which we wish to express is the tenacity with which the organism preserves its specificity. At least this specificity can be modified, if at all, only by gradual

[1] J. Loeb, *Amer. Journ. Physiol.*, 1900, Vol. 3, p. 441.

degrees; and any theory of growth or heredity must assign some definite basis for this characteristic conservatism. We have suggested above that this basis is the tendency of similarly constituted compounds to segregate in the formation of aggregates, and in this way to form structures which determine the direction of metabolism. But such an hypothesis explains only the *resemblance* of an organism to its parent; it does not indicate how the proliferative process itself is carried out. It appears, in fact, that two separate groups of problems are involved in the theory of heredity—the one relating to the conditions determining the resemblance to the parent stock, the other relating to the nature of the physiological mechanism by which the living substance (apart from its special nature) increases its quantity or *grows* at the expense of materials taken from the surroundings. Such growth is a physiological activity requiring the expenditure of energy, and it cannot be considered apart from its relation to the other physiological, *i. e.*, functional, activities of the organism. The nature of this latter relation now calls for special consideration.

The general significance of the normal functional activity of the living system as one of the chief factors in the formation of its characteristic structure, or in structure-forming metabolism generally, has been insufficiently regarded by writers on heredity. In general, any normally active tissue maintains itself or grows, while an inactive tissue remains stationary or undergoes regression, even if supplied with an abundance of oxygen and food-material; this last is well shown in a voluntary muscle whose innervation has been interrupted. It is clear that increased functional activity involves an increase of constructive as well as of destructive metabolism; and conversely the subnormal metabolism accompanying inactivity is associated with subnormal construction, which may even fall below destruction, with regression or atrophy as a result. The control which function exercises upon the building-up of living structure is seen perhaps most clearly in higher organisms, and especially in tissues like voluntary muscle, whose activity is intermittent and subject to much variation. In this case the effects of exercise in promoting growth and of disuse in causing regression are

familiar to all; and essentially similar conditions are found in other tissues and organs. Functional hypertrophy following excessive activity, and regression or atrophy following prolonged inactivity, are both well-known phenomena; for example, compensatory hypertrophy in heart muscle is a frequent result of valvular lesions, and one kidney increases in size if the other is removed. In general it would appear that any physiological function can reach and preserve its highest perfection only through continual repetition; and this very condition implies that decline must follow inactivity if the latter is prolonged beyond a norm. And since every function has some organized structure as its correlate, the same considerations apply to whatever structures are concerned in the function in question. The modifications which the central nervous system undergoes in association with the process of learning afford instances of an essentially similar kind; practise facilitates the repetition of any complex voluntary action, *i. e.*, perfects the structural and other adjustments underlying the function;[1] while any accomplishment, intellectual or other, declines with disuse. These examples may suffice to illustrate the general principle under consideration. It seems clear that the physico-chemical mechanisms—whatever their nature may be—controlling functional activity are in some intimate relation to those determining growth. The above facts seem to imply that both classes of physiological processes are simultaneously and equally under the control of some more general set of conditions characteristic of living substance in general. We shall now consider this possibility in more detail.

Claude Bernard has pointed out how essential it is in any living system—if the system is to continue to exist—that there should be a relation of interdependence between the processes of destruction and of repair, of such a kind that any destructive or dissimilatory process sets in motion automatically the contrary process of repair.[2] All functional activity involves break-

[1] This is the basis of the phenomenon of *memory*. Hering has discussed briefly the relations between memory and heredity in his well-known address on "Memory as a General Function of Organized Matter," Vienna Academy, 1870; English translation by Open Court Publishing Company, Chicago, 1897.

[2] "Leçons sur les phénomènes de la vie," Vol. 1, Chapter 3.

down of organized material, and apparently some disintegration of cell-structure then always takes place, for protein metabolism is increased—even though slightly under good nutritive conditions —by increased muscular work.[1] Hence for normal regulation of cell-activity it is essential that a compensatory or constructive series of processes should be aroused into action by the same conditions that stimulate or call forth the destructive or energy-yielding activity. "Functional breakdown in living material is itself the precursor and instigator of the renovation accomplished by the formative process, which works silently and obscurely in the interior of the tissue" (*i. e.*, without evident external manifestation, in contrast to the destructive process). "Losses are thus repaired as rapidly as they are caused, and since equilibrium tends to re-establish itself as soon as it is destroyed, the normal composition of the living body is maintained."[2] Bernard also recognizes that this process of restitution

[1] It is now amply demonstrated that increased muscular work in higher animals leads to little or no increase in breakdown of protein (as indicated by N-excretion), provided the non-nitrogenous food-constituents are sufficient in quantity, especially the carbohydrates. If the food contains sufficient protein for maintenance, but carbohydrate and fat are deficient, there may be a considerable increase in N-excretion, but typically not enough to account for the increased energy-production on the basis of oxidation of protein; in this case the surplus of energy comes from the non-nitrogenous reserves of the organism. Carbohydrate is especially effective as a protein-sparer, a fact indicating that in the construction of protein it plays an essential part. It is also the chief source of muscular energy; and the fact that vigorous muscular work, involving active consumption of sugar, is the chief condition for the normal growth of the tissue, shows that the energy required for this growth—*i. e.* for the chemical and structural syntheses involved—is derived from the oxidation of sugar. The possible metabolic changes concerned in this process cannot be considered in an article like the present. But that carbohydrate is essential for the assimilation of amino-acids and other nitrogen compounds in both animals and plants is indicated by a large body of recent and older investigation. Thus for the assimilation of amino-acids by yeast and moulds sugar is indispensible (*cf.* the series of papers by F. Ehrlich, *Biochem. Zeitschr.*, 1906, Vol. 1, p. 8; 1908, Vol. 8, p. 438; 1909, Vol. 18, p. 391; 1911, Vol. 36, p. 477); similarly in higher plants the synthesis of protein from amides in germination requires the presence of carbohydrates (for a brief summary of the facts *cf.* Jost's "Physiology of Plants," p. 175). The work of Loewi, Lüthje and others has shown the great importance of carbohydrates in the synthesis of protein from amino-acids in higher animals; there is also clear evidence that derangement of carbohydrate metabolism (*e. g.*, in pancreatic or other diabetes) interferes very directly with the synthesis of protein (*cf.* Chapter 9 of Cathcart's "Physiology of Protein Metabolism" for a general review of this subject and literature).

[2] "Leçons sur les phénomènes de la vie," Vol. 1, p. 127.

involves not only a chemical synthesis, but also a morphological synthesis, *i. e.*, a rebuilding of organized structure. The constructive and the destructive processes are inseparable; synthesis is life, whether during rest or activity. Hence the rate of construction must be regarded as ultimately under the same kind of control as the rate of destruction, even though the latter is more obviously subject to modification under the usual conditions of life (as in stimulation, voluntary action, etc.).[1] As instances of the initiation of organic construction by conditions whose primary effect is to stimulate, *i. e.*, to *increase* the energy-yielding dissimilation, Bernard cites the awakening of dormant germs or hibernating animals by rise of temperature or other stimulating condition;[2] the resumption of growth and other processes involving increased assimilation illustrates the constant, though it may be indirect, nature of the interconnection. An apposite present day-illustration of the same phenomenon would be the initiation of development in unfertilized eggs by a temporary cytolytic action. But one does not need to search for instances; the reciprocal interdependence of assimilation and dissimilation is seen everywhere in organisms; how essential this relation is for the preservation of life appears, for example, in the general fact that in all animals increased muscular or other activity hastens the onset of *hunger*, *i. e.*, of the condition necessary for supplying the raw material for construction. The maintenance of a balance between the two kinds of metabolic processes constitutes probably the most fundamental of the various types of organic regulation.

There is no doubt that a general regulatory condition of this kind exists in all organisms; the problem is to determine the essential physico-chemical conditions upon which it depends. We must regard the living system primarily as one in which the synthesis of both chemical substance and organized structure is controlled by functional activity. And during the growth and development of the system, *i. e.*, at the periods when synthetic

[1] Bernard gives direct experimental evidence of the identity of the conditions controlling growth with those controlling stimulation by showing that growth (*e. g.* in seedlings) may be anæsthetized under the same conditions as the different forms of irritability. *Cf.* his chapter on Irritability, Leçons, Vol. 1, p. 267.

[2] *Cf.* Leçons, Vol. 1, Chapter 2, p. 110.

activity predominates, a similar dependence of formative activity on function must exist. This is the kind of relation emphasized recently by Child, when he describes the developing organism not as being first constructed and then functioning, after the manner of a machine, but as constructing itself *by* functioning.[1] Growth and development are peculiar in that specific construction overbalances destruction, and that the synthesized material, as it accumulates, adopts a definite organization. But this accumulation of structure is itself the expression or result of active functioning, in which energy is freed, just as growth is such an expression in a muscle which has been exercised. Apparently we must conclude that part of this energy is expended in the work of synthesizing and arranging the specific structural material of the organism or cell. We have already seen that this specific material consists essentially of protein. We are thus brought back to the question: what are the conditions under which protein is synthesized in the living cell and deposited as structure?

No very definite or certain answer can be given at present to this question. But we seem to be in a position to rule out certain possibilities, and perhaps to affirm others. First we must note more particularly the significance of the long recognized fact that many vital syntheses require the addition of energy to the synthesized compounds; this is seen, for instance, in the formation of fats from proteins and carbohydrates. Now since such syntheses, where compounds of higher chemical potential are built up from those of lower, take place continually in all cells, it appears highly probable that their conditions are also the main conditions of synthesis in general, and that a subordinate importance is to be attached to the purely enzymatic type of synthesis. Both experience and theory show that the latter is limited to the formation of compounds in which little change of energy accompanies the transformation;[2] hence it is plainly insufficient to meet the normal requirements of constructive metabolism. Some kind of mechanism would seem to be indicated in which energy derived from oxidation or other chemical source is applied

[1] C. M. Child, "Individuality in Organisms." University of Chicago Press, 1915, p. 16.

[2] *Cf.* Höber's "Physikalische Chemie der Zelle und der Gewebe," 1914, p. 677.

to perform the work of chemical and structural synthesis. Enzymes may facilitate or direct certain kinds of combinations, and in this way they may be important as accessory factors in the constructive process; but the essential controlling factors are evidently of a more active, *i. e.*, work-performing, kind. And since these factors vary in their activity with function, it follows that the conditions controlling the degree and rate of functional activity—*i. e.*, generally speaking, the conditions of stimulation—must at the same time be the conditions controlling the specific constructive processes.[1] It is true that construction does not always run parallel with destruction, the rate of which may often temporarily exceed that of repair; and at times nutritive or other conditions may render complete replacement impossible; or at other times construction may preponderate, as in growth. Nevertheless an interdependence of the kind indicated unquestionably does exist; and apparently we must infer that part of the energy freed in the oxidation (or other energy-yielding decomposition) which performs the work of function is applied, in some manner as yet unknown, to build up the material required for maintenance or further growth.

If we adopt this general hypothesis, we must reject as entirely insufficient the conception of growth as being analogous to a process of crystallization, or as being determined by syntheses of the enzymatic kind; and we are led to look for some other type of process in which the formation and deposition of structural material is controlled by energy set free in chemical change. This process must be capable of variation in rate, of interruption and renewal, and of reversal,—if it is to correspond to such

[1] This is indicated by Bernard's already cited observation that anæsthetics arrest growth-processes reversibly in the same manner as they inhibit stimulation or other forms of functional activity,—a fact suggesting that physico-chemical changes of the same nature control both growth and the response to stimulation. If this is true, it seems probable that the structures primarily concerned in stimulation are also those primarily concerned in construction, *i. e.*, the site or *locus* of both constructive and destructive processes is the same, the two representing reverse phases of the same process. On such a view the idea that special regions of the cell (*e. g.*, the nucleus) are the exclusive seat of syntheses would have to be abandoned. There is, however, much evidence that the nucleus is necessary for the continuance of synthetic processes; possibly it gives rise to certain substances which are required for the maintenance of the structures more immediately concerned in the specific syntheses.

features of organic growth as the variation of the latter with the conditions (*e. g.*, temperature or the supply of food and oxygen), its dependence on function, and the possibility of regression. Further, it must be a process not necessarily peculiar to living organisms, although apparently taking place under especially favorable conditions in these systems, and it must be able to effect either chemical decompositions or syntheses. All of these peculiarities seem to point to some physico-chemical process of the general nature of electrolysis as underlying the synthetic activity of organisms. In other words the possibility presents itself that electrosynthesis is the chief method of construction in the living system.

The main physiological facts which appear to me to favor this hypothesis are briefly as follows. All functional activity is associated with the formation of electrical circuits between different regions of the cell or organism. The currents of these bioelectric circuits are in many cases sufficiently intense to produce marked physiological effects upon other cells or tissues (stimulation, etc.), and presumably they have similar effects upon other regions of the same cell; the transmission of the effects of local excitation appears in fact to be due to an action of this kind. In general we observe vital functions to be profoundly influenced—accelerated, inhibited, or initiated—by electrical influence; and since function involves specific construction, the constructive process must be subject to similar influence. Experimental data upon the influence of the electric current on growth processes are as yet comparatively few; but galvanotropism is well known in plants, and with properly devised experimentation could probably be shown to be widespread. The control of growth processes by the electric current offers in fact a largely untouched field of investigation, which would probably yield results not only of great theoretical interest but of practical importance as well (*e. g.*, as possibly affording a means of controlling malignant growths, etc.).

But perhaps the clearest indications that the organic formative processes are under the control of electrical conditions are seen in the striking resemblances which certain types of electrolytic deposit show, both in their structural character and in the con-

ditions influencing their formation, to the structures arising by normal growth in organisms. The two types of phenomena exhibit many close and, as it seems to me, highly significant parallels. Inorganic structures resembling vegetative growths are seen not only in the formation of lead or tin "trees" from metallic zinc immersed in solutions of salts of these metals, but they are shown in an especially striking form in those cases where the local process of electrolysis gives rise to precipitates which form coherent membranes or otherwise exhibit colloidal character. In a recent paper I have described the structure and conditions of formation of such precipitation-structures in some detail, and have discussed the reasons for their resemblance to organic growths.[1] In solutions of potassium ferricyanide, especially those containing egg-albumin or other protective colloid, pieces of metallic iron, zinc, or copper produce characteristic filamentous or quasi-cellular outgrowths, consisting of precipitation-membranes of the ferricyanide of the metal used, which resemble strongly certain definite organic types of growth like mould-hyphæ. These structures grow out into the solution from the anodic regions of the metallic surface; hence their formation may be accelerated, retarded, or suppressed at will by varying the character of the local circuits determining the rate at which the ions of the metal enter solution. A region of (*e. g.*), iron which is actively forming precipitation-filaments will at once cease this action if it is rendered the cathode in another intercepting local circuit,—*e. g.*, by the contact of zinc or other baser metal at a neighboring point; or conversely it may be rendered still more active—*i. e.*, more strongly anodic—by increasing the intensity of the local circuit in which it acts as anode,—*e. g.*, by the adjacent contact of a nobler metal (*e. g.*, platinum) or carbon.[2] It is especially to be noted that the relations between the different electrode-regions of such local circuits are *reciprocal*, as regards the character of the chemical changes there taking place; this is inevitable, since in general the electrochemical processes at any anode are the reverse of those at the cathode. Hence the formation of filaments at one region of the metallic surface appears to have the effect of *inhibiting* their formation at another ad-

[1] BIOLOGICAL BULLETIN, 1917, Vol. 33, p. 135.

[2] *Loc. cit.*, p. 148.

joining region. A similar reciprocality of influence is especially characteristic of physiological processes, such as excitation and inhibition, *e. g.*, in the central nervous system; and it is also well known to be characteristic of various processes of growth and regeneration in both animals and plants.[1] This is why (for example) cutting off a tubularian head enables an adjoining region of the stem to form a new hydranth; the region where the new growth takes place has been removed (by the operation) from the inhibiting influence of the original hydranth. Similarly a short piece of iron wire which is in contact with a piece of zinc will not form filaments in ferricyanide solution until the zinc is detached or otherwise rendered inactive. Cutting away the zinc thus initiates the development of filaments from the iron;[2] the structure-forming process had previously been inhibited by the activity at the zinc, which on account of its greater tendency to send ions into solution alone forms filaments while the two metals are in contact. To express the matter biologically: the zinc seems actively to appropriate the available structure-forming material (ferricyanide), and in so doing prevents the iron from utilizing this material to form filaments. Similarly the hydranth, with its higher rate of metabolism, acts as the chief structure-forming region in the tubularian, and inhibits structure-formation of the same kind in its vicinity.[3] It corresponds, in this sense, to the anodal metal in the local electrical couple of zinc and iron. The growth-initiating consequences following physiological isolation—to use Child's concise and illuminating expression[4]—may thus be instructively simulated by means of an inorganic model of this kind.

These and similar parallels appear to indicate that *the same type of process* is concerned in the structure-formation in the two kinds of system, otherwise so entirely unlike in character.[5] If

[1] *Loc. cit.*, pp. 156, 163.

[2] *Loc. cit.*, pp. 152 *seq.*

[3] This is an example of the dominance or control of formative processes by those regions having the highest rate of metabolism: *cf.* Child's "Senescence and Rejuvenescence," Chapter 9, p. 210; also "Individuality in Organisms," Chapter 5.

[4] *Loc. cit.*

[5] It is a question whether an electric current passing between any semi-permeable water-insoluble phase and the adjoining aqueous solution can do so otherwise than by a process of ionization (or deionization) at the boundary, *i. e.*, by a process

this is true, the transmission of the structure-forming or growth-inhibiting influence is in both cases due to the formation of electrical circuits between the influenced and the influencing regions. In their morphological details and in their chemical composition the structures formed are, needless to say, widely different in the living system and in its inorganic model, although in certain peculiarities of physico-chemical constitution—especially the cellular and filamentous character of the formations and the part played in both by semipermeable membranes—the precipitation-structures and the living systems show significant resemblances. A precipitation-structure of a definite chemical composition even shows a certain morphological specificity, *i. e.*, the structures formed from zinc are characteristic in their appearance and different from those formed from iron or copper. We may say that under the influence of the metal the ferricyanide of the solution is transformed into structure of a definite kind. And this structure, once formed, becomes the condition of formation of other similar structure.[1]

To complete the resemblance to a growing plant-filament or other proliferating living system, the structures thus formed ought to be capable, after isolation, of forming more structure of the same kind. This is of course not the case with the precipitation-filaments, taken by themselves, since the connection with the metal is essential; but the difference may be regarded as due mainly to incidental conditions. The growing system is in fact not constituted by the filaments *alone*, but by the combination of filaments, metal and solution; the formative process depends upon the interaction of all three. Something analogous may be said to be true of the growing organism; in a spore placed in a

involving electrolysis. This is what takes place in the passage of a current between a metallic surface and a solution; in this case the addition or abstraction of electric charges to or from substances present at the boundary is what forms the essential condition of the electrolysis there taking place. The cell-surface is similarly water-insoluble, and semi-permeability is characteristic; yet it allows the passage of the electric current, although with a somewhat high and variable resistance. The facts of polar stimulation, polar disintegration, etc., indicate that where the current *enters* the cell-surface it produces different chemical effects from where it *leaves*, just as in electrolysis at metallic surfaces.

[1] *Cf.* the description of the mode of formation of precipitation-filaments, *loc. cit.*, pp. 143–144.

culture-medium the structure of the germ, its chemical composition, and the chemical composition of the culture-medium, are all equally essential factors in the resulting growth-process. The main difference is that each living cell, as soon as formed, is capable of acting as a similar center of transformation when transferred to another culture-medium; *i. e.*, *all* of the necessary parts of the proliferating system are multiplied equally; and so far we have been unable to produce any artificial systems having such properties. If we were to succeed in doing so, it is probable that such systems would exhibit a much closer resemblance to living organisms than any of the inorganic models hitherto used for comparisons of the above kind.

Obviously these fundamental resemblances between the two types of system under comparison do not preclude infinite differences in the details of structure, chemical composition, and activity; but I am at present insisting upon the resemblances because of the desirability of determining the *class* to which the organic formative processes belong. The characteristic plasticity and responsiveness of living matter undoubtedly depend upon the fundamental features of its physico-chemical constitution. Starting with living material of this peculiar type of self-regulating structure and chemical composition, the developmental process has in the course of time become so evolved and perfected that it now builds up with unfailing regularity the most complex of organisms from the food and other materials furnished to the germ from the surroundings. But the possibility of this development has depended upon certain general pecularities of physico-chemical constitution present from the beginning in the living formative substance itself; and my aim in the present and preceding papers is to indicate what seem to me the most essential of these peculiarities.

The case of higher organisms presents numerous problems of a more special kind, and most investigators in the field of heredity have given their chief attention to these problems. It seems clear that in these organisms other and more special mechanisms of hereditary coördination and control have been superposed upon the elementary physico-chemical mechanism which conditions the fundamental proliferative activity. The fact that in

higher animals particular cell-structures like chromosomes may become essential regulatory or determinative factors, controlling the detailed character of the developmental proliferation, is in no sense inconsistent with the general point of view here presented. All protoplasmic structures as they originate must influence formative metabolism, as has been so ably pointed out by Child; and there is every evidence that the chromosomes have a peculiarly intimate relation to the distribution of form-determining factors. Recognition of the part played by hormones in development is also consistent with the present view. What we are now attempting, however, is not to define the special mechanisms governing the course of development in the higher metazoa, but to indicate the nature of the more general physico-chemical mechanism, common to all forms of living matter, which forms the basis of its characteristic self-conserving and proliferative properties. Any conception of the essential constitution of living matter must first of all take its constant and fundamental distinguishing peculiarities into account. Once the living material has come into existence, with such properties as these, it may serve as the basis for the development of diversity and complexity of all kinds, as has in fact occurred in the course of evolution.